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## ORIGINAL ARTICLE

# Clinical and economic impact of compression in the acute phase of deep vein thrombosis

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## Essentials

- The value of compression therapy in acute phase of deep vein thrombosis is still unclear.
- Patients with deep vein thrombosis received acute compression hosiery, bandaging, or none.
- Acute compression reduces irreversible skin signs related to post thrombotic syndrome.
- Compression hosiery may be the preferred choice for the acute phase

**Summary.** *Background:* The effectiveness of compression therapy in the acute phase of deep vein thrombosis (DVT) is not yet determined. *Objectives:* To investigate the impact of compression therapy in the acute phase of DVT on determinants of the Villalta score, health-related quality of life (HRQOL), and costs. *Patients/Methods:* Eight hundred and sixty-five patients with proximal DVT (substudy of the IDEAL DVT study) received, immediately after DVT diagnosis, either no compression,

multilayer bandaging, or hosiery. In the acute phase and 3 months after diagnosis, HRQOL was determined by use of the EQ-5D, SF6D, and VEINES-QoL intrinsic method (VEINES-QoL<sup>int</sup>). At 3 months, signs and symptoms were assessed for the total and separate items of the Villalta score, and healthcare costs were calculated. *Results:* The compression groups had lower overall objective Villalta scores than the no-compression group (1.47 [standard deviation (SD) 1.570] and 1.59 [SD 1.64] versus 2.21 [SD 2.15]). The differences were mainly attributable to irreversible skin signs (induration, hyperpigmentation, and venectasia) and pain on calf compression. Subjective and total Villalta scores were similar across groups. Differences in HRQOL were only observed at 1 month; HRQOL was better for hosiery (EQ-5D 0.86 [SD 0.18]; VEINES-QoL<sup>int</sup> 0.66 [SD 0.18]) than for multilayer compression bandaging (EQ-5D 0.81 [SD 0.23]; VEINES-QoL<sup>int</sup> 0.62 [SD 0.19]). Mean healthcare costs per patient were €417.08 (€354.10 to €489.30) for bandaging, €114.25 (€92.50 to €198.43) for hosiery, and €105.86 (€34.63 to €199.30) for no compression. *Conclusions:* Initial compression reduces irreversible skin signs, edema, and pain on calf compression. Multilayer bandaging is slightly more effective than hosiery, but has substantially higher costs, without a gain in HRQOL. From a patient and economic perspective, compression hosiery would be preferred when initial compression is applied. Trial registration: IDEAL DVT study ClinicalTrials.gov number, NCT01429714.

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**Keywords:** costs; prevention; quality of life; signs and symptoms; venous thrombosis.

## Introduction

Deep vein thrombosis (DVT) is a potential debilitating and life-threatening disease, with an annual incidence of 1–2 per 1000 people [1]. Complaints related to DVT can vary from mild to severe, with DVT recurrence and pulmonary embolism being the most severe consequences [2]. The long-term complication is known as post-thrombotic syndrome (PTS), and develops in 20–50% of patients within 2 years after DVT diagnosis [3,4]. PTS is an irreversible condition that comprises a combination of patient-reported symptoms such as pain and cramps, and objective signs such as edema and venous ulcers. The severity of each of the signs and symptoms is assessed with the Villalta score. According to the current consensus ISTH scoring method, a sum score of  $\geq 5$  at least 6 months after DVT is considered to show that PTS is present [5]. It has been shown that quality of life is reduced in patients with DVT in general [6,7], and in PTS patients in particular [8]. Moreover, DVT complicated by PTS is associated with higher costs than DVT without PTS [9,10].

The main, although disputed, form of preventive therapy for PTS is the use of elastic compression stockings (ECS) (class III, ankle pressure of 40 mmHg) for a period of up to 2 years following DVT [3,4,11]. Generally, ECS are applied as soon as leg edema is resolved, which usually takes 2–6 weeks. Currently, there is no consensus regarding what the preferred mode of treatment is in the time frame between DVT diagnosis and ECS application. There are three possible approaches to bridge the acute phase: no compression, the application of multilayer compression bandages, or the use of thigh-high compression hosiery (Mediven Struva 35 mmHg). Up to now, only a limited number of, mainly smaller, studies have explored the general effects of compression therapy in the acute phase of DVT. A randomized controlled trial with 69 patients compared the effect of multilayer bandaging with no compression, and found an improvement in clinical symptoms and a decrease in leg circumference 7 days after intervention, but no effect was found after 1 month and 3 months, or in relation to PTS after 1 year [12]. Beneficial effects of compression therapy immediately after thrombosis were observed by others [13]. A study in 53 patients that compared compression with inelastic bandaging or ECS in addition to daily walking exercise versus no compression combined with bed rest showed that, at 9 days, quality of life was significantly better in the compression group. Patients who received compression reported significantly less pain and swelling. [14].

On the basis of the outcomes of these few studies, compression in the acute phase of DVT seems to have beneficial effects in terms of diminished signs and symptoms; however, conclusive answers are lacking, as the studies were relatively small. Therefore, the current study was aimed at comparing the effects of no compression, multi-layer bandaging and compression hosiery in the acute phase of DVT on the separate items as well as the overall Villalta score. In addition, the present study aimed to assess the impact of acute compression therapy on quality of life, and to estimate the initial healthcare costs related to acute compression therapy following DVT diagnosis.

## Methods

### *Study design and population center*

This study was an *a priori*-planned substudy of the IDEAL DVT study, which has been described in detail previously [15]. In short, the IDEAL DVT study was a multicenter randomized controlled trial that started in April 2011 and was concluded in July 2017. The study involved 865 patients with objectively confirmed proximal DVT without venous insufficiency or previous DVT from 12 medical centers across the Netherlands and two in Italy.

The study compared individualized duration of ECS use with standard long-term (24 months) duration. Three prespecified treatment protocols that were agreed upon before study start described which form of compression therapy was applied in the acute phase of DVT in each individual center in the time frame between DVT diagnosis and the start of ECS use [16]. All included patients received thigh-high short stretch multilayer compression bandaging applied by trained healthcare professionals, thigh-high elastic compression hosiery (Mediven Struva 35 mmHg), or no compression; this initial treatment was not randomized, but was allocated according to the centers' prespecified treatment protocols. The randomization for the IDEAL DVT study was stratified by center in order to ensure an equal distribution of initial treatments. If compression was initiated, this was performed within 24 h of DVT diagnosis. A week prior to the outpatient clinic visits, the patients filled out a questionnaire on quality of life and costs. The first (baseline) questionnaire was filled out within a week after the inclusion. The language of the overall questionnaire was Dutch for the Dutch centers and Italian for the Italian centers.

### *Outcomes*

Determinants of the Villalta score at 3 months after DVT were assessed. These included five patient-rated symptoms (pain, cramps, heaviness, paresthesia, and itching) and six physical signs (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia,

and redness). All items were graded for intensity on a 4-point scale: 0 points when there were no deviations from normal, 1 point if the signs or symptoms were mild, 2 points if they were moderate, and 3 points if they were severe. Symptoms of the subjective Villalta score were rated and filled out by patients in the questionnaire. The objective items were assessed and filled out at each study visit by a medical doctor or a research nurse in the case report form.

Health-related quality of life (HRQOL) was assessed in the acute phase of DVT (1 week after inclusion) and 3 months after DVT diagnosis. HRQOL was determined with two generic questionnaires and one disease-specific questionnaire: the EQ-5D, the Short Form Health Survey version 2 (SF36), and the disease-specific Venous Insufficiency Epidemiological and Economic Study (VEINES-QoL). The EQ-5D covers five dimensions of generic HRQOL (mobility, self-care, usual activity, pain, and anxiety). Health state preferences, expressed as utility scores, are calculated with a scoring function based on the preferences of a general public (2997 respondents from the UK) and scores on each item [17]. The range of the score is  $-0.59$  to  $1$ , where  $-0.59$  suggests a health state worse than death,  $0$  refers to death, and  $1$  indicates perfect health. The SF36 consists of 36 questions covering several health domains: physical functioning, physical role functioning, emotional role functioning, social role functioning, mental health, bodily pain, vitality, and general health perceptions. A utility score derived from the SF36, the SF6D, was calculated [18]. On the basis of the literature, a difference of  $0.076$  in EQ-5D scores and a difference of  $0.041$  in SF6D scores were considered to be clinically relevant differences [19].

The VEINES-QoL contains 26 items on the following topics: DVT-related symptoms, limitations in daily activities, time of day when the leg complaint is of greatest intensity, changes in leg complaints over the last year, and the psychological impact of the leg complaints [20]. The VEINES-QoL average score was calculated on the basis of the intrinsic method (VEINES-QoL<sup>int</sup>) as recommended by Bland *et al.* [21], whereby each item score ( $i$ ) is recoded to  $(i - 1)/(k - 1)$ , with  $k$  referring to the number of categories. Based on this formula, each item's score has a value between  $0$  and  $1$ , and the average is the final score. This intrinsic method makes it possible to compare average quality of life scores with other quality of life scores. For all quality of life instruments, a higher score suggests better quality of life.

The following cost domains were estimated: visits (including transportation costs) to the general practitioner, general practice center out of hours care, or medical specialist, the use of painkillers, home care nursing demands, and costs of compression material use. Unit costs were multiplied by the patient-reported frequency of resource use, with recall periods of 4 weeks for nursing and 8 weeks for other items (reported at 3 months after DVT

diagnosis), and divided by the total number of patients per group. Unit costs were based on the guidelines on healthcare costs drafted by the Dutch Health Authority [22]. The costs of the compression bandages were based on amounts as indicated in the Dutch G-standard March 2017 [23]. The costs of the compression hosiery were €25 to €55 per item [24].

### Statistical analysis

All statistical analyses were performed with spss version 23, with a  $P$ -value of  $\leq 0.05$  being considered to be statistically significant. The association between different compression strategies and separate signs and symptoms forming the Villalta score were analyzed, as were the total objective, total subjective and the complete Villalta scores, by the use of ANCOVA for comparison of multiple groups and regression analysis for two-group comparisons. Split plot analysis of variance for repeated measures was performed for assessment of the time effect on quality of life scores. Analyses were adjusted for center and baseline variables that differed significantly among groups. Costs were bootstrapped to obtain 95% credibility intervals. Sensitivity analyses were performed with complete data. Subanalysis with regard to assessment of signs and symptoms was performed in patients with iliofemoral DVT. All analyses were also performed with the bandaging group and hosiery group taken together as one compression group.

### Results

The percentages of missing data attributable to withdrawals, loss to follow-up, disease and late exclusion were 4.3%, 1.4%, 2.8%, and 1.0%, respectively. Analyses with complete cases and cases with some missing data on the items showed no statistically significant difference. Therefore, imputation of missing data was not performed.

### Subject characteristics

The study population consisted of 865 patients. The average inclusion date was  $18.4 \pm 12$  days after DVT diagnosis. A total of 668 patients (78.0%) received initial compression, of whom 415 (48.5%) were in the multilayer bandaging group, and 253 (29.6%) were in the compression hosiery group. However, 16 of 253 (6.3%) patients in the hosiery group required multilayer bandaging because of leg complaints. One hundred and eighty-eight patients (21.9%) received no initial compression. Table 1 shows the baseline characteristics for the study population. Overall, the mean age was  $57.2 \pm 15.1$  years. The percentage of male patients was 58.2%. The average body mass index was  $27.9 \pm 5.2 \text{ kg m}^{-2}$ . DVT located in the left leg was seen in 451 (52.7%) of patients. Previous contralateral DVT was seen in 81 (9.5%) patients. The



baseline characteristics across groups were mostly similar; a statistically significant difference among the groups was found only with regard to the nature and location of DVT. In the no-compression group, 108 (57.4%) patients had unprovoked DVT, in comparison with 296 (71.3%) in the multilayer bandaging group and 175 (69.2%) in the hosiery group ( $P = 0.017$ ). DVT was located in the common femoral vein in 33.5% of patients in the no-compression group, as compared with 19.0% in the multilayer bandaging group and 16.6% in the hosiery group ( $P < 0.001$ ).

### Signs and symptoms

Figure 1 and Table 2 show the Villalta scores at 3 months after DVT diagnosis. The total Villalta score, the total subjective Villalta score and all individual items constituting the subjective part were not significantly different among groups. Significant differences were observed for the objective part of the Villalta score; the total objective score in the compression groups combined ( $1.52 \pm 1.59$ ,  $P < 0.001$ ) was lower than that in the no-compression group ( $2.21 \pm 2.15$ ). The scores for the separate compression groups were also lower than that in the no-compression group:  $1.47 \pm 1.57$  in the multilayer bandaging group ( $P < 0.001$ ), and  $1.59 \pm 1.64$  in the hosiery group ( $P < 0.001$ ). Additionally, statistically significant differences between the compression group and the no-compression group were seen for mainly irreversible signs, i.e. skin induration, hyperpigmentation, and venectasia, and for pain upon calf compression. Those with bandaging had statistically significant lower scores on the objective items skin induration and hyperpigmentation than those with hosiery (respectively:  $0.04 \pm 0.27$  versus  $0.15 \pm 0.44$ ,

$P = 0.002$ ; and  $0.11 \pm 0.37$  versus  $0.20 \pm 0.46$ ,  $P = 0.028$ ).

The results of the subgroup analysis using only data of patients with iliofemoral thrombosis were in line with the results for the entire population. There were no differences in the total Villalta score or the subjective part of the Villalta score. The total objective part was significantly lower in the compression groups than in the no-compression group ( $1.78 \pm 2.17$  versus  $2.20 \pm 2.17$ ,  $P = 0.025$ ). The efficacy of compression was entirely based on multilayer compression bandaging. In this group, a significantly lower total objective Villalta score with fewer irreversible skin signs, i.e. indurations, hyperpigmentation, and venectasia, was observed than in the no-compression group ( $1.52 \pm 1.60$  versus  $2.2 \pm 2.17$ ,  $P = 0.017$ ) and the hosiery group ( $2.25 \pm 1.72$ ,  $P = 0.158$ ).

### Quality of life

Table 3 shows the quality of life scores in the acute phase and at 3 months after DVT. There were no statistically significant differences in HRQOL for all compression versus no compression. In the acute phase, however, the hosiery group had statistically significantly higher scores than the bandaging group on the EQ-5D ( $0.86 \pm 0.18$  versus  $0.81 \pm 0.23$ ,  $P = 0.015$ ) and the VEINES-QoL<sup>int</sup> ( $0.66 \pm 0.18$  versus  $0.62 \pm 0.19$ ,  $P = 0.030$ ). Three months after DVT, no statistically significant differences were observed. Split plot analysis of variance for repeated measures showed no statistically significant difference over time (SF6D,  $P = 0.470$ ; EQ-5D,  $P = 0.263$ ; and VEINES-QoL<sup>int</sup>,  $P = 0.136$ ). This means that, if the two time points are combined, no differences in the compression groups exist.

**Table 1** Baseline characteristics across compression groups

|   | Overall<br>( <i>N</i> = 856) | Multilayer bandaging<br>group ( <i>N</i> = 415) | Compression hosiery<br>group ( <i>N</i> = 253) | No-compression<br>group ( <i>N</i> = 188) | <i>P</i> -value*  |
|---|------------------------------|---|--|---|-------------------|
| Characteristics                             |                              |   |  |   |                   |
| Age (years),<br>mean (SD)                   | 57.2 (15.1)                  | 58.0 (15.5)                                     | 56.5 (14.1)                                    | 56.4 (15.6)                               | 0.307             |
| Male, <i>n</i> (%)                          | 498 (58.2)                   | 244 (58.8)                                      | 148 (58.5)                                     | 106 (56.4)                                | 0.850             |
| BMI (kg m <sup>-2</sup> ) (SD)              | 27.9 (5.2)                   | 28.1 (5.0)                                      | 27.9 (5.1)                                     | 27.7 (5.8)                                | 0.646             |
| DVT in left leg, <i>n</i> (%)               | 451 (52.7)                   | 223 (53.7)                                      | 128 (50.6)                                     | 100 (53.2)                                | 0.726             |
| Previous contralateral<br>DVT, <i>n</i> (%) | 81 (9.5)                     | 40 (9.6)  | 19 (7.6)                                       | 22 (11.7)                                 | 0.169             |
| Unprovoked DVT,<br><i>n</i> (%)             | 579 (67.6)                   | 296 (71.3)                                      | 175 (69.2)                                     | 108 (57.4)                                | <b>0.017</b>      |
| DVT location, <i>n</i> (%)                  |                              |   |  |   |                   |
| Popliteal                                   | 421 (49.2)                   | 224 (54.0)                                      | 130 (51.4)                                     | 67 (35.6)                                 | <b>&lt; 0.001</b> |
| Femoral                                     | 236 (27.6)                   | 108 (26.0)                                      | 80 (31.6)                                      | 48 (25.5)                                 |                   |
| Common femoral                              | 184 (21.5)                   | 79 (19.0)                                       | 42 (16.6)                                      | 63 (33.5)                                 |                   |
| Unknown                                     | 15 (1.6)                     | 4 (1.0)   | 1 (0.4)  | 10 (5.3)                                  |                   |

BMI, body mass index; DVT, deep vein thrombosis; SD, standard deviation. \* $\chi^2$  test for categorical variables; one-way ANOVA for continuous variables. *P*-values refers to differences among groups or the difference in distribution of thrombus location among groups. Values in bold indicate statistical significance.

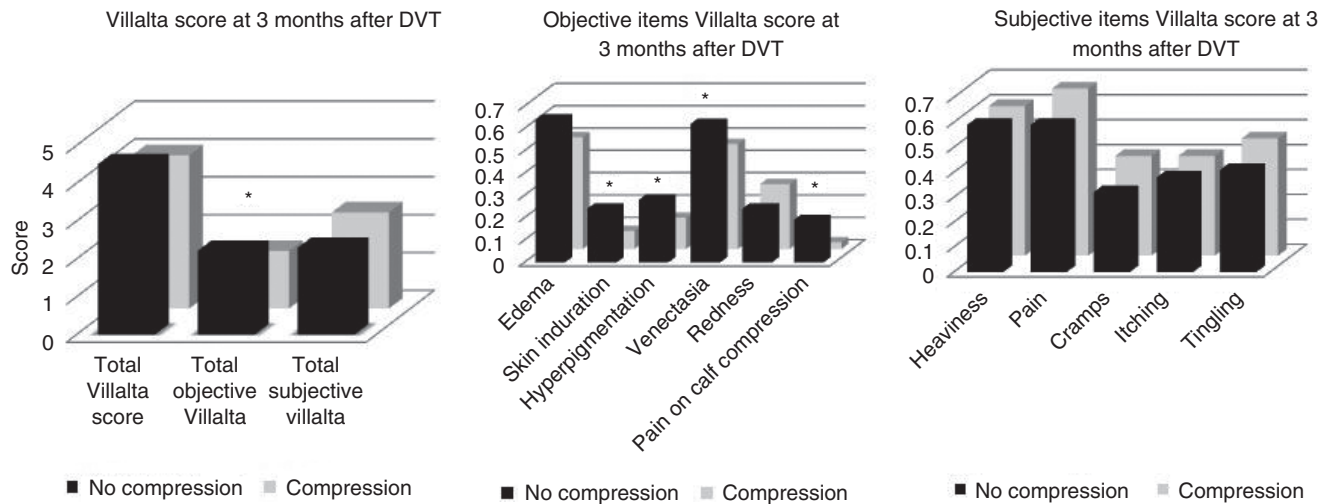


Fig. 1. Total Villalta scores and the separate items of the Villalta score at 3 months after diagnosis of deep vein thrombosis

Table 2 Villalta scores at 3 months after the diagnosis of deep vein thrombosis

|                          | All compression (N = 668) |      | No compression (N = 188) |      | No compression versus all compression P-value | Multilayer bandaging (N = 415) |      | Multilayer bandaging versus no compression P-value | Compression hosiery (N = 253) |      | Compression hosiery versus no compression P-value | Multilayer bandaging versus compression hosiery P-value |
|--------------------------|---------------------------|------|--------------------------|------|---|--------------------------------|------|--|-------------------------------|------|---|---|
|                          | Mean                      | SD   | Mean                     | SD   |   | Mean                           | SD   |  | Mean                          | SD   |   |   |
| Total objective Villalta | 1.52                      | 1.59 | 2.21                     | 2.15 | < <b>0.001</b>                                | 1.47                           | 1.57 | < <b>0.001</b>                                     | 1.59                          | 1.64 | < <b>0.001</b>                                    | 1.000   |
| Edema                    | 0.50                      | 0.69 | 0.64                     | 0.79 | 0.163   | 0.53                           | 0.73 | 0.222  | 0.45                          | 0.62 | <b>0.018</b>                                      | 0.513   |
| Skin induration          | 0.08                      | 0.35 | 0.24                     | 0.54 | < <b>0.001</b>                                | 0.04                           | 0.27 | < <b>0.001</b>                                     | 0.15                          | 0.44 | 0.067   | <b>0.002</b>  |
| Hyperpigmentation        | 0.14                      | 0.41 | 0.28                     | 0.56 | < <b>0.001</b>                                | 0.11                           | 0.37 | < <b>0.001</b>                                     | 0.20                          | 0.46 | 0.141   | <b>0.028</b>  |
| Venous ectasia           | 0.47                      | 0.71 | 0.62                     | 0.76 | < <b>0.001</b>                                | 0.51                           | 0.79 | 0.138  | 0.40                          | 0.55 | <b>0.002</b>                                      | 0.149   |
| Redness                  | 0.29                      | 0.55 | 0.24                     | 0.55 | 0.154   | 0.27                           | 0.54 | 1.000  | 0.33                          | 0.56 | 0.461   | 0.649   |
| Pain on calf compression | 0.03                      | 0.20 | 0.19                     | 0.52 | < <b>0.001</b>                                | 0.01                           | 0.11 | < <b>0.001</b>                                     | 0.07                          | 0.30 | < <b>0.001</b>                                    | 0.076   |
| Total subjective score   | 2.54                      | 2.74 | 2.29                     | 2.49 | 0.162   | 2.46                           | 2.55 | 1.000  | 2.65                          | 3.03 | 0.556   | 1.000   |
| Heaviness                | 0.60                      | 0.86 | 0.59                     | 0.77 | 0.652   | 0.60                           | 0.83 | 1.000  | 0.62                          | 0.90 | 1.000   | 1.000   |
| Pain                     | 0.67                      | 0.93 | 0.59                     | 0.85 | 0.354   | 0.68                           | 0.93 | 0.924  | 0.67                          | 0.95 | 1.000   | 1.000   |
| Cramps                   | 0.40                      | 0.72 | 0.32                     | 0.65 | 0.086   | 0.37                           | 0.66 | 1.000  | 0.45                          | 0.80 | 0.263   | 0.463   |
| Itching                  | 0.40                      | 0.68 | 0.38                     | 0.71 | 0.501   | 0.37                           | 0.65 | 1.000  | 0.44                          | 0.74 | 1.000   | 0.649   |
| Tingling                 | 0.47                      | 0.71 | 0.41                     | 0.67 | 0.210   | 0.45                           | 0.69 | 1.000  | 0.49                          | 0.74 | 0.645   | 1.000   |
| Total Villalta score     | 4.05                      | 3.34 | 4.50                     | 3.68 | 0.168   | 3.94                           | 3.08 | 0.154  | 4.25                          | 3.72 | 1.000   | 0.734   |

SD, standard deviation. Analyses were adjusted for baseline differences and patient center. Values in bold indicate statistical significance.

## Costs

Healthcare costs in the compression groups are shown in Table 4. The mean total costs per patient were highest for the bandaging group (€417.08, 95% confidence interval [CI] €354.10 to €489.30), followed by the hosiery group (€114.25, 95% CI €92.50 to €198.43); the costs were lowest for the no-compression group (€105.86, 95% CI €34.63 to €199.30). The differences in costs across groups were mainly attributable to costs related to compression material use and home care nursing demands, which were both highest in the bandaging group and lowest in the no-compression group.

## Discussion

Compression in the acute phase of DVT reduces the occurrence of pain on calf compression, and the incidence of hyperpigmentation, venectasia, and skin induration, which are irreversible skin signs that are associated with PTS. Consequently, the objective part of the Villalta score was significantly decreased in patients who received initial compression therapy. These effects, although small in absolute terms, were significantly more pronounced in the group of patients who received multilayer bandaging. No differences among groups were seen with regard to the subjective items of the Villalta score and the sum total Villalta score.

**Table 3** Quality of life across groups in the acute phase of deep vein thrombosis (DVT) and 3 months after DVT diagnosis

|                           | All compression |      | No compression |      | All compression versus no compression<br><i>P</i> -value | Multilayer bandaging group |      | Multilayer bandaging versus no compression<br><i>P</i> -value | Compression hosiery group |      | Compression hosiery versus no compression<br><i>P</i> -value | Multilayer bandaging versus compression hosiery<br><i>P</i> -value |
|---------------------------|-----------------|------|----------------|------|--|----------------------------|------|---|---------------------------|------|--|--|
|                           | Mean            | SD   | Mean           | SD   |  | Mean                       | SD   |   | Mean                      | SD   |  |  |
| Acute phase of DVT        | <i>N</i> = 171  |      |                |      |  | <i>N</i> = 385             |      |   | <i>N</i> = 218            |      |  |  |
| VEINES-QoL <sup>int</sup> | 0.64            | 0.18 | 0.62           | 0.17 | 0.553  | 0.62                       | 0.19 | 1.000   | 0.66                      | 0.18 | 0.192  | <b>0.030</b>   |
| SF6D                      | 0.62            | 0.06 | 0.62           | 0.06 | 0.809  | 0.62                       | 0.06 | 1.000   | 0.61                      | 0.06 | 0.758  | 1.000  |
| EQ5D                      | 0.83            | 0.21 | 0.82           | 0.23 | 0.587  | 0.81                       | 0.23 | 1.000   | 0.86                      | 0.18 | 0.230  | <b>0.028</b>   |
| Three months after DVT    | <i>N</i> = 668  |      |                |      |  | <i>N</i> = 415             |      |   | <i>N</i> = 253            |      |  |  |
| VEINES-QoL <sup>int</sup> | 0.73            | 0.16 | 0.72           | 0.16 | 0.657  | 0.72                       | 0.16 | 1.000   | 0.74                      | 0.16 | 1.000  | 0.901  |
| SF6D                      | 0.63            | 0.06 | 0.62           | 0.06 | 0.359  | 0.63                       | 0.06 | 1.000   | 0.63                      | 0.05 | 0.993  | 1.000  |
| EQ-5D                     | 0.86            | 0.22 | 0.84           | 0.23 | 0.303  | 0.85                       | 0.22 | 1.000   | 0.87                      | 0.21 | 0.786  | 1.000  |

SF, Short Form Health Survey; SD, standard deviation; VEINES-QoL, Venous Insufficiency Epidemiological and Economic Study. Analyses were adjusted for baseline differences and for center. Higher values indicate better quality of life. Score scale: EQ-5D, -0.59 to 1; SF6D and VEINES-QoL<sup>int</sup>, 0 to 1. Values in bold indicate statistical significance.

The exact pathophysiology of PTS is not yet known; however, it is assumed that, in the acute phase, venous hypertension caused by thrombus obstruction and subsequent inflammation and edema are central features. External compression reduces the vein diameter and improves venous flow velocity, thereby improving venous outflow and reducing edema and inflammation. Therefore, compression in the acute phase may reduce inflammation and secondary skin changes associated with PTS [25–27], as is also suggested by our results.

It might be argued whether these small differences are clinically relevant. In absolute terms, the majority of patients had low Villalta scores, with no or minimal signs and symptoms. However, if the percentages of moderate and severe signs between groups are compared, then the differences become prominent. As these differences involve irreversible skin signs, they may be considered to be clinically relevant. Overall, patients experienced relatively few complaints. This lack of contrast between treatment groups for the subjective part of the Villalta score was reflected in the similar outcomes for quality of life assessments. In the initial phase, however, HRQOL was significantly better for hosiery than for bandaging.

The costs and burdens related to multilayer bandaging are higher than those related to no compression and hosiery. The question is, what amount of expenditure and discomfort is justified in relation to the outcome? Therefore, it is of the utmost importance to be able to identify patients at the highest risk, as patients at risk for PTS constitute a heterogeneous group.

So far, only a few studies have assessed the merits of compression in the acute phase. The numbers of participants were rather small, i.e. 69, 53 and 73 patients [12]

[14,28]. Moreover, those studies did not assess the signs and symptoms of PTS individually. Despite the mentioned limitations, they too found some beneficial effects of compression in the acute phase of DVT.

The strengths of our study are its size and its multicenter nature, as it involved both academic and non-academic centers, and the fact that quality of life and cost aspects were also assessed. A limitation of our study design is the lack of randomization of patients for the three preventive options. However, each center offered the same therapy to all patients from that center, so the choice of intervention could be considered to be quasi-randomized. Furthermore, analyses were adjusted for center and baseline differences between treatment groups.

It is important to determine which of the three mentioned options (multilayer bandaging, compression hosiery, or no initial compression) should be chosen, not only because their effects on clinical symptoms might differ, but also because the costs related to each option can vary substantially. Multilayer bandaging requires the help of (para)medical professionals and more medical materials, owing to regular redressing, than compression hosiery, which patients need to purchase only once and can apply by themselves.

We found that, for the subgroup of patients with iliofemoral DVT, that compression hosiery was not effective, but that multilayer bandaging provided a significant reduction in irreversible skin signs. For the specific subgroup of patients with iliofemoral DVT, the costs and burdens of multilayer bandaging might therefore be weighted differently and favour multilayer bandaging.

In conclusion, there are significant reductions in irreversible signs, edema and pain on calf compression

**Table 4** Mean healthcare costs per patient per group

| Cost category                                     | Multilayer compression bandaging ( <i>N</i> = 415) |                    |             |                        | Compression hosiery ( <i>N</i> = 253) |             |                       |                | No compression ( <i>N</i> = 188) |             |                       |                |
|---|--|--------------------|-------------|------------------------|---------------------------------------|-------------|-----------------------|----------------|----------------------------------|-------------|-----------------------|----------------|
|   | Unit costs (€)                                     | Number of patients | Mean volume | Mean costs (€)         | Number of patients                    | Mean volume | Mean costs (€)        | Mean costs (€) | Number of patients               | Mean volume | Mean costs (€)        | Mean costs (€) |
| <b>Healthcare</b>                                 |  |                    |             |                        |                                       |             |                       |                |                                  |             |                       |                |
| General practitioner (total)                      |  | 37                 |             | 7.68                   | 34                                    |             | 8.62                  |                | 17                               |             | 6.13                  |                |
| Visit   | 33   | 32                 | 0.143       | 4.72                   | 26                                    | 0.189       | 6.25                  |                | 14                               | 0.122       | 4.04                  |                |
| Home visit  | 50   | 6                  | 0.034       | 1.73                   | 0                                     | 0.000       | 0.00                  |                | 1                                | 0.006       | 0.32                  |                |
| Telephone contact                                 | 17   | 10                 | 0.055       | 0.93                   | 15                                    | 0.129       | 2.19                  |                | 8                                | 0.081       | 1.38                  |                |
| Patient travel costs                              | 2.66–43.14   | 21                 | 11.315      | 6.58                   | 12                                    | 0.209       | 6.46                  |                | 11                               | 6.186       | 6.83                  |                |
| General practice center out of hours care (total) |  | 6                  |             | 1.44                   | 5                                     |             | 0.99                  |                | 1                                |             | 0.24                  |                |
| Visit   | 33   | 3                  | 0.030       | 1.00                   | 1                                     | 0.017       | 0.57                  |                | 1                                | 0.006       | 0.20                  |                |
| Home visit  | 50   | 0                  | 0.000       | 0.00                   | 0                                     | 0.000       | 0.00                  |                | 0                                | 0.000       | 0.00                  |                |
| Telephone contact                                 | 17   | 2                  | 0.013       | 0.23                   | 1                                     | 0.017       | 0.29                  |                | 0                                | 0.000       | 0.00                  |                |
| Patient travel costs                              | 2.66–43.14   | 5                  | 2.787       | 14.87                  | 4                                     | 0.043       | 6.83                  |                | 1                                | 0.012       | 6.83                  |                |
| Medical specialist (total)                        |  | 71                 |             | 39.75                  | 49                                    |             | 37.22                 |                | 16                               |             | 13.49                 |                |
| Visit   | 91   | 71                 | 0.417       | 38.00                  | 49                                    | 0.388       | 35.34                 |                | 16                               | 0.142       | 12.91                 |                |
| Patient travel costs specialist                   | 2.66–43.14   | 59                 | 14.317      | 11.63                  | 41                                    | 9.223       | 10.50                 |                | 13                               | 0.219       | 7.14                  |                |
| <b>Medication use</b>                             |  |                    |             |                        |                                       |             |                       |                |                                  |             |                       |                |
| Box of painkillers                                | 1.00–4.95  | 19                 | 1           | 6.98                   | 13                                    | 1           | 8.73                  |                | 2                                | 1           | 9.00                  |                |
| Compression material*                             | 40–66.91   | 415                | 3320        | 267.64                 | 253                                   | 253†        | 40                    |                | 0                                | 0           | 0.00                  |                |
| Home care nursing costs                           | 73   | 49                 | 1.723       | 125.84                 | 5                                     | 0.478       | 35.54                 |                | 9                                | 1.381       | 100.87                |                |
| Total costs, mean (95% CI)                        |  |                    |             | 417.08 (354.10–489.30) |                                       |             | 114.25 (92.50–198.43) |                |                                  |             | 106.39 (34.63–199.30) |                |

CI, confidence interval. \*Costs of compression material are based on the assumption that a change of multilayer bandaging is performed twice weekly for a duration of 4 week. †Of the 253 patients who were originally prescribed compression hosiery, 16 received multilayer compression bandaging because of leg complaints.



associated with initial compression therapy in any form, and there is clinically significantly better HRQOL for initial compression with compression hosiery than for multilayer bandaging. Multilayer bandaging is, overall, slightly more effective than compression hosiery, but without the gain in HRQOL, and at a significantly higher cost. Compression hosiery is a relatively cheap, easy to use and safe alternative to multilayer bandaging in all patients. Therefore, both from both a patient perspective and an economic perspective, compression hosiery would be the preferred choice when initial compression is applied in unselected patients.

## Addendum

M. A. Joore and A. J. ten Cate-Hoek were responsible for the concept and design. E. E. Amin, M. A. Joore, and A. J. ten Cate-Hoek were responsible for the analysis and/or interpretation of data. Each author contributed to the development of the manuscript, reviewed and commented on each draft, and approved the version to be published. All authors were responsible for critical writing or revision of the intellectual content.

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## Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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